Remarks/Arguments

Claims 1, 13, 14, 26, 27, 49, and 50 have been amended to include the subject matter of Claims 9, 11 and 12. Claims 9, 11, and 12 have been canceled. Claims 1-8, 10, and 13-52 are pending in the application.

Claim Rejections-35 U.S.C. §102(e)

The Examiner has rejected claims 1-7, 11-17, 21-26, 28, 49 and 51 under 35 U.S.C. §102(e) as being anticipated by Jensen et al., U.S. Pat. No. 6,043,214 ("Jensen"). Applicants have amended independent claims 1, 26, and 49 to include elements of the invention that are not disclosed by Jensen. Accordingly, the presently claimed invention is not anticipated by Jensen, and the Applicants respectfully request that the rejection under 35 U.S.C. 102(e) be withdrawn.

Claim Rejections-35 U.S.C. §103

The Examiner has rejected claims 1-10, 12-17, 21-26, 28, 49, and 51-52 under 35 U.S.C. §103(a) as being unpatentable over Jensen in view of Maa et al. (U.S. Pat. No. 6,284,282, "Maa"). The Examiner states that Jensen lacks specific disclosure on tap density of the powder particles. The Examiner states that Maa discloses a method of freeze spray drying proteins for pharmaceutical administration, and that the protein particles of Maa have a tap density of less than about $0.8g/cm^3$, with a tap density of less than about $0.4g/cm^3$ being preferred. The Examiner also states that Maa discloses proteins which include insulin. The Examiner concludes that it would have been obvious to a person of ordinary skill in the art at the time the invention was made given the general teachings of powder formulation of insulin of Jensen to have looked in the art for specific particle characteristics such as tap density as disclosed by Maa et al, with reasonable expectations of preparing effective formulations for pulmonary delivery by improving their dispersibility, absorbability and respirability. Applicants respectfully disagree with the Examiner's conclusion.

Jensen states that the invention disclosed therein is directed towards a method of producing a therapeutic powder formulation by a process involving precipitation of an

aqueous solution comprising insulin and an enhancer to produce a powder formulation (see, column 2, lines 41-54). Jensen states that the ability to precipitate insulin and an enhancer is surprising because the enhancer normally inhibits precipitation (see, column 2, lines 36-40). Jensen also states that the powder formulation produced by the process disclosed therein has enhanced features, such as stability and flowability, as compared to the same formulation produced by spray drying, freeze spray drying, vacuum drying and open drying. Jensen further states that the process of the invention disclosed therein is preferably carried out so as to obtain a substantially crystalline product (see, column 4, lines 4-8).

Applicants submit that Jensen's disclosure of a process for preparing a formulation by precipitation teaches away from the presently claimed invention. Jensen specifically states that that the powders resulting from the precipitation process described therein are different from, and provide advantages over, similar compositions that have been spray dried or freeze dried. Applicants have amended the instant claims to recite additional features that the powder compositions of the instant invention comprise, such as tap densities of less than 0.4 g/cm^3 , aerodynamic diameters of from about 1 to about 5 microns and particle sizes of about 5 to about 30 microns. The ability to control the range of the tap density, aerodynamic diameter and particle size of powders of the invention relies on the spray-drying process by which the powder compositions of the present invention are produced. In contrast, Jensen's disclosed precipitation process does not provide a means for controlling or achieving the tap density, aerodynamic size or average particle size of the powder formulations resulting from the precipitation process. The precipitation process disclosed by Jensen yields crystals. These crystals are the result of allowing a spontaneous amorphous precipitate to rest for a period of time to allow the formation of crystals which are then dried to form the dry powder disclosed therein. The crystals resulting from the precipitation process described by Jensen are whatever size and shape that the precipitation process yields. Jensen does no more than measure the size of the resulting crystals. One skilled in the art would not look to a precipitation process such as that disclosed by Jensen, if the skilled practitioner was

concerned about controlling the tap density, aerodynamic diameter and particle size of the final powder product as is presently claimed.

Similarly, Jensen teaches away from Maa. Maa discloses that the desired tap density, aerodynamic diameter and geometric diameters of particles disclosed therein may be achieved by freeze spray drying, and that particles having such specified characteristics can be achieved through manipulation of certain parameters of the freeze spray drying procedure (see Maa, column 4, line 60 to column 5 line 29). As Jensen discloses a fundamentally different process that teaches away from the formulations produced by freeze spray drying disclosed in Maa, there is no motivation to combine Jensen with Maa as the Examiner has done (Tec Air, Inc. v. Denso Manufacturing Michigan Inc., 192 F.3d 1353, 1360, 52 USPQ2d 1294, 1298 (Fed. Cir. 1999) (``There is no suggestion to combine ... if a reference teaches away from its combination with another source")). Even if one were motivated by Maa to prepare particles having the listed properties, Maa does not teach how one would accomplish this goal using the process of Jensen. Therefore, Applicants respectfully request that the Examiner withdraw the obviousness rejection of the claims in view of the combination of Jensen and Maa.

The Examiner has rejected claims 1-17, 21-28, 30-40, 44-52 under 35 U.S.C. §103(a) as being unpatentable over Jensen in view of Weers et al. (6,309,623). The Examiner states that Jensen lacks the specific disclosure of tap density and geometric diameter of the insulin particles. The Examiner states that Weers teaches stabilized preparations for the delivery of a bioactive agent to the respiratory tract of a patient using a metered dose inhaler. The Examiner further states the particles disclosed in Weers have a mean geometric diameter of less than 20 micrometers or less than 10 micrometers and most preferably less than about 5 micrometers. The Examiner also states that Weers teaches that the particles have a tap density of less than 0.5 g/cm^3 , a mean aerodynamic diameter of less than about 3 micrometers and the particle preparations are suitable for deep lung delivery. Finally, the Examiner states that Weers also discloses inhalation formulations that include insulin. The Examiner concludes that it would have been obvious to a person of ordinary skill in the art at the time the invention was made given

the general teachings of powder formulation of insulin of Jensen to have looked in the art for specific particle characteristics such as tap density as disclosed by Maa et al. (Applicants assume that the Examiner meant to say "Weers et al". and not "Maa et al.".), with reasonable expectations of preparing effective formulations for pulmonary delivery by improving their dispersibility, absorbability and respirability. Applicants respectfully disagree with the Examiner's conclusion.

As with the Examiner's combination of Jensen and Maa above, Jensen teaches away from the stabilized preparations disclosed in Weers. As discussed above, Jensen's dry powders are produced by a precipitation process that results in dry powders that are mostly crystalline particles. Jensen specifically states that that the powders resulting from the precipitation process described therein are different from, and provide advantages over, similar compositions that have been spray dried or freeze dried.

In contrast, Weers discloses that the stabilized preparations described therein are the result of the use of hollow and/or porous perforated microstructures having particular characteristics such as specific tap densities, aerodynamic size and geometric diameters (see Weers, column 4, lines 5-10, all of columns 13 and 14). The crystalline particles resulting from the precipitation process disclosed by Jensen are relatively dense, solid and non-porous as compared to the hollow and/or porous perforated microstructures of Weers. Weers further discloses that the hollow and/or porous perforated microstructures disclosed therein are the result of a process that provides control over a number of parameters to allow for the formation of such hollow, and/or porous perforated microstructures (see column 22, lines 12-32) comprising the desired tap density, aerodynamic diameter and geometric diameters. Examples of suitable processes disclosed by Weers include spray drying (column 21, lines 12-22) or freeze drying (lyophilization) (column 25, lines 62-column 26, line 18) of microparticle reagents, or certain emulsion procedures (column 26, lines 18- 33). A precipitation process such as that disclosed in Jensen does not, by its nature, provide one skilled in the art with the means to control the formation of the crystals from the precipitate such that the resulting crystals are hollow and/or porous and possess desired tap density, aerodynamic and geometric sizes of the stabilized formulations of Weers.

Therefore, one skilled in the art would not be motivated to combine Jensen and Weers, as Jensen teaches away from a process and a product such as that described in Weers. Accordingly, Applicants respectfully submit that the Examiner withdraw the obviousness rejection of the present invention in view of the combination of Jensen and Weers.

The Examiner has rejected claims 18-20, 29 and 41-43 under 35 U.S.C. §103(a) as being unpatentable over Jensen in view of the International Ingredient Dictionary and Handbook. The Examiner states that Jensen lacks specific disclosure on the inclusion of carboxylic acid in the formulation, but that Jensen teaches that hydrocholoric acid is added to the formulation to adjust the pH. The Examiner asserts that the International Ingredient Dictionary and Handbook discloses that carboxylic acids such as citric acids are well known pH adjusters in pharmaceutical formulations. The Examiner concludes that one skilled in the art would have been motivated to replace hydrochloric acid of Jensen with citric acid to perform a pH adjusting function and that the expected result would be a successful formulation for the pulmonary delivery of insulin.

In response, Applicants respectfully submit that the combination of Jensen and the International Ingredient Dictionary and Handbook does not make obvious the presently claimed invention. Jensen does not disclose or suggest particles having the tap density, aerodynamic and geometric particle sizes of the presently claimed formulations from which claims 18-20, 29 and 41-43 depend. The International Ingredient Dictionary and Handbook does not provide what the Jensen reference lacks. Accordingly, applicants respectfully request that the rejection of the claims in view of the combination of Jensen and the International Ingredient Dictionary and Handbook be withdrawn.

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned at (978) 251-3509.

Respectfully submitted,

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